Original Article

Respiratory complications associated with ketamine anesthesia for ophthalmic procedures following intraocular pressure measurement in children

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Abstract

Background: We compared respiratory complications (RCs) in children who received intramuscular (IM) versus intravenous (IV) or no ketamine for intraocular pressure (IOP) measurement to test our observation that IM ketamine is associated with higher incidence of RCs.
Materials and Methods: We analyzed 149 eye examinations under anesthesia with ketamine in 27 patients and 263 non-ketamine examinations under anesthesia in 81 patients using a mixed effects logistic regression model.
Results: IM ketamine was strongly associated with increased odds of RCs compared to no ketamine (odds ratio (OR): 20.23, $P < 0.0001$) and to IV ketamine (OR: 6.78, $P = 0.02$), as were higher American Society of Anesthesiologists (ASA) classification (OR: 2.60, $P = 0.04$), and the use of volatile agents (OR: 3.32, $P = 0.02$).
Conclusion: Further studies should be conducted to confirm our observation of increased RCs with IM ketamine.

Key words: Adverse events, child, infant, intravenous agents, ophthalmology

Introduction

Measurement of intraocular pressure (IOP) in children requires examination under anesthesia (EUA). The ideal anesthetic agent for this purpose is ketamine because it does not affect patient's IOP.[1-3] Previous studies have shown ketamine to be safe.[4-6] However, other studies have also noted that ketamine is sometimes associated with respiratory complications (RCs) and emesis.[7-9] At our institution, perioperative staff noted that children who received intramuscular (IM) ketamine appeared to experience RCs more frequently than those who received intravenous (IV) ketamine or no ketamine. The aim of this study was to compare the occurrence of RCs between patients who received IM ketamine versus IV ketamine or no ketamine.

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Materials and Methods

After Institutional Review Board approval, we conducted a retrospective study of children 12 years or younger who underwent EUA for IOP measurement at our institution. Potential patients who had received ketamine were identified by reviewing every procedure performed by one of the authors (B.E.) between 2/1/2006 and 7/31/2009 in the electronic medical record (Epic, Epic Systems Corporation, Verona, WI). All patients who received either IM or IV ketamine for IOP measurement were included in the study. During the study period, each patient may have had more than one EUA. For each EUA, the patient's weight, comorbidities (asthma, sleep apnea, and history of difficult airway), presence of upper respiratory infection, American Society of Anesthesiologists (ASA) physical status classification, method of airway control, anesthetic agent/s, initial and total doses of ketamine, anesthesiologist, and occurrence of RCs were recorded and entered into a database. RCs were defined as airway obstruction, laryngospasm, bronchospasm, and apnea. These

complications were further divided into two categories: Major and minor. If a RC resulted in the nursing staff activating the code team as documented in the perioperative note, it was considered major, and the rest were considered minor.

Patients who did not receive ketamine were identified by reviewing EUAs performed by seven other surgeons who did not use ketamine for IOP measurement within the same time period. Three matched non-ketamine patients were selected for each ketamine patient based on their age at the time of their first EUA (divided into three groups: 0-1; 2-6; and 7-12 years) and gender. The three to one ratio was used to ensure this study was sufficiently powered based on our preliminary estimates. The same set of variables was collected for them.

Patients in the ketamine group received either IM or IV ketamine with glycopyrrolate before their eyes were examined and IOPs were measured. Depending on the procedures following IOP measurements which ranged from more in-depth examination to suture removal to complex ocular surgeries, they either received repeat doses of ketamine or they were switched to volatile anesthetics and/or propofol. Instrumentation of the airway if any occurred after the IOPs were obtained. Patients in the non-ketamine group received volatile anesthetics, propofol, or benzodiazepine before their IOPs were measured immediately after their administration. In all groups, the patient's method of airway control (endotracheal tube (ETT), laryngeal mask airway (LMA), or natural airway) was determined by the anesthesiologist based on the patient's condition and the type and length of the procedures following the IOP measurements.

Patient characteristics were summarized using descriptive statistics and compared using Pearson's χ^2 or Fisher's exact test among ketamine groups for categorical variables, and analysis of variance (ANOVA) for continuous variables. A mixed effects logistic regression model was used to assess the association between the occurrence of RCs and the use of ketamine while accounting for correlations due to multiple EUAs in the same patient, matching of ketamine and non-ketamine patients, and controlling for other potential confounding variables.

Results

A total of 149 ketamine EUAs in 27 patients and 263 non-ketamine EUAs in 81 patients were included in the study over the 30-month period. Of the ketamine patients, 41% (11) received IM ketamine only, 22% (6) received IV ketamine only, and 37% (10) received both IM ketamine and IV ketamine. All patients received glycopyrrolate with their initial dose of IM or IV ketamine. Table 1 shows the characteristics of ketamine and non-ketamine patients. Table 2 summarizes the characteristics of ketamine and non-ketamine EUAs.

The median dose for IM ketamine was 8 mg/kg with an interquartile range (IQR) of 4 mg/kg (6-10). The median dose for IV ketamine was 2.75 mg/kg with an IQR of 2 mg/kg (2-4). One patient accidentally received 40 mg/kg IM instead of the intended 4 mg/kg dose. He was admitted as an inpatient for overnight observation, but he did not have any complications intraoperatively or postoperatively except for prolonged sedation. The average length of total anesthesia time for IM ketamine, IV ketamine, and non-ketamine EUAs were 1.44 (SD, 0.73), 1.45 (SD, 0.85), and 1.03 (SD, 0.60) h, respectively. The non-ketamine patients received either propofol alone (2.3%), inhalational anesthesia alone (57.0%), a combination of both propofol and inhalational anesthesia (40.0%), or benzodiazepine only (0.7%).

Table 1: Characteristics of ketamine and non-ketamine patients

Demographic variables	Ketamine (*N* = 27)	Non-ketamine (*N* = 81)	*P*-value
Age at 1st EUA in years, mean (SD)	1.9 (2.3)	1.8 (2.3)	0.86
Gender: Male (%)	59.3	59.3	1.00
Gender: Female (%)	40.7	40.7	1.00
Weight in kg, mean (SD)	9.76 (5.34)	10.28 (6.31)	0.67

EUA = Examination under anesthesia, SD = Standard deviation

Table 2: Characteristics of ketamine EUAs vs non-ketamine EUAs

EUA variables	IM ketamine EUAs (*N* = 101) (%)	IV ketamine EUAs (*N* = 48) (%)	Non-ketamine EUAs (*N* = 263) (%)	*P*-value
Use of volatile agent/s (Sevoflurane, isoflurane, and desflurane)	53 (52.5)	21 (43.8)	255 (97.0)	<0.0001*
Desflurane	7/53 (13.2)	0/21 (0)	23/255 (9.0)	0.175
Use of propofol	64 (63.4)	38 (79.2)	111 (42.2)	<0.0001*
Endotracheal tube (ETT)	21 (20.8)	11 (22.9)	50 (19.0)	0.797
Laryngeal mask airway (LMA)	30 (29.7)	19 (39.6)	193 (73.4)	<0.0001*
Natural airway (no airway instrumentation)	50 (49.5)	18 (37.5)	20 (7.6)	<0.0001*
ASA class I/II	70 (69.3)	27 (56.3)	148 (56.3)	0.068

**Statistically significant (P < 0.05), EUA = Examination under anesthesia, ASA = American Society of Anesthesiologists, IM = Intramuscular, IV = Intravenous*

Overall, RCs occurred in 22.8% (23/101) of IM ketamine EUAs, 4.2% (2/48) of IV ketamine EUAs, and 2.7% (7/263) of non-ketamine EUAs [Table 3]. No nystagmus was noted in any of the patients. Table 4 summarizes the absolute number of each type of RCs in each study group, and Table 5 summarizes the methods of airway within each type of RCs. For laryngospasm, five cases occurred upon extubation, two cases occurred in the postanesthesia care unit, and two cases occurred intraoperatively. The only case of bronchospasm occurred intraoperatively in an intubated patient while being repositioned for intraocular photography. Major complications occurred in two EUAs and both involved the same patient who received IM ketamine. There were no risk factors that would have definitively increased his risk for RCs. At the time of these procedures, he carried the diagnosis of Axenfeld-Rieger anomalies of both eyes with hypertelorism, bilateral sensorineural hearing loss, and Eustachian tube dysfunction. No other craniofacial or cardiopulmonary abnormalities were present. In the multivariable model after adjusting for other variables, IM ketamine was associated with increased odds of RCs as compared to no ketamine (odds ratio (OR) = 20.23, $P < 0.0001$) and to IV ketamine (OR = 6.78, $P = 0.02$). There was no statistical difference between IV ketamine and no ketamine ($P = 0.23$) [Table 6]. Additionally, patients with ASA class III and IV were more likely to experience RCs as compared to ASA class I and II (OR = 2.60, $P = 0.04$), and administration of volatile agent/s (sevoflurane, isoflurane, and desflurane) in all patients (IM ketamine, IV ketamine, and no ketamine) was also associated with an increased odds of RCs (OR = 3.32, $P = 0.02$) when compared to those who did not receive volatile agents. Diseases in ASA class III and IV patients included retinoblastoma, uncontrolled bilateral glaucoma, retinopathy of prematurity, retinal detachment, Axenfeld-Rieger syndrome, Sturge-Weber syndrome, cytomegalovirus (CMV) retinitis, Coats' disease, developmental delay, and Peter's anomaly with corneal graft rejection. Desflurane was used in 30 EUAs [Table 2] and two RCs were associated with desflurane; both occurred after IM ketamine administration. Occurrence of RCs was not higher with desflurane use compared to non-desflurane use [Table 3].

Other variables including age, weight, gender, use of propofol (yes vs no), length of procedure, and method of airway control (ETT vs LMA vs natural airway) were tested but excluded from the final multivariate model as they were not significant predictors nor confounders for the association between RC and ketamine use.

Discussion

The rates of RCs associated with ketamine reported in previous studies were 1.4-4.0% for IM ketamine [4,9] and 1.3-8.3% for IV ketamine.[6,10,11] The higher rate of RC associated with IM ketamine (22.8%) in this study could be due to higher than usual doses of IM ketamine and/or differences in the study population. Our subjects had a mean age less than 2 years where the incidence of RC is likely to be higher, whereas other studies were primarily done in adults. In contrast to a previous study showing no difference between IM ketamine and IV ketamine[10] our study corroborates the findings of Melendez and Bachur[12] that IM ketamine is significantly associated with increased odds of RCs although there are differences in our study population. Their patients had an average age of 6.4 years, and all of them were emergency department patients whose chief complaints were predominantly injury related (bone fractures and facial/oral lacerations). Almost 50% of patients in that study received atropine, whereas none of our patients received atropine. Patients in the ketamine group were less likely to receive airway protection with either LMA or ETT [Table 2]. However, this does not appear to be a confounding factor as the occurrence of airway obstruction and apnea was similar between the patients who received LMA or ETT and those who did not have any airway protection [Table 5]. Although differences in surgical technique, duration of procedures and patient positioning between B.E. and the other seven surgeons may have been confounding variables

Table 3: Incidence of respiratory complications by subgroups and clinical variables

Clinical variables	IM ketamine EUAs (*N* = 101) (%)	IV ketamine EUAs (*N* = 48) (%)	Non-ketamine EUAs (*N* = 263) (%)	*P*-value
RCs overall	23/101 (22.8)	2/48 (4.2)	7/263 (2.7)	<0.0001*
ASA I/II	13/70 (18.6)	2/27(7.4)	1/148 (0.7)	<0.0001*
ASA III/IV	10/31 (32.3)	0/21 (0)	6/115 (5.2)	<0.0001*
Use of volatile agent/s	17/53 (32.1)	1/21 (4.8)	7/255 (2.7)	<0.0001*
Desflurane	2/7 (28.6)	0/0	0/23 (0)	0.0483
Isoflurane or sevoflurane	15/46 (32.6)	1/21 (4.8)	7/232 (3.0)	<0.0001*
No volatile agent	6/48 (12.5)	1/27 (3.7)	0/8 (0)	0.0798

**Statistically significant (P < 0.05), EUA = Examination under anesthesia, IM = Intramuscular, IV = Intravenous, RC = Respiratory complications, ASA = American society of anesthesiologists*

Table 4: Absolute number of complications by category

Complications	IM Ketamine	IV Ketamine	Non-Ketamine
Laryngospasm	6	2	1
Bronchospasm	1	0	0
Airway obstruction	9	0	3
Apnea	7	0	3

IM = Intramuscular, IV = Intravenous

Table 5: Complications according to airway management

Complications	Laryngeal mask airway	Endotracheal tube	Natural airway
Laryngospasm	6	2	1
Bronchospasm	0	1	0
Airway obstruction	5	0	6
Apnea	4	4	3

Table 6: Odds ratios (OR) for respiratory complications

Variables	OR (95% CI)	*P*-value
Ketamine use		<0.0001*
IM vs no ketamine	20.23 (6.13, 66.74)	<0.0001*
IV vs no ketamine	2.98 (0.50, 17.67)	0.23
IM vs IV	6.78 (1.36, 33.82)	0.02*
ASA class 3/4 vs 1/2	2.60 (1.03, 6.54)	0.04*
Volatile agents (Y vs N)	3.32 (1.18, 9.32)	0.02*

**Statistically significant (P < 0.05), IM = Intramuscular, IV = Intravenous, ASA = American society of anesthesiologists, CI = Confidence interval, Y = Yes, N = No*

that contributed to the difference between IM ketamine and no ketamine, this seems unlikely as there was no statistical difference in the odds of RCs between B.E.'s IV ketamine patients and non-ketamine patients of the other seven surgeons. Furthermore, this would not explain the difference between IM ketamine and IV ketamine as B.E. serves as her own control. Future prospective studies can eliminate this potential confounder by using only one surgeon.

Although desflurane may cause airway irritation,[13] it does not appear to be a predictor for RCs in this study. Other potential confounders including active upper respiratory infection and other comorbidities are unlikely contributors given their low prevalence compared to the occurrence of RC.

In conclusion, our findings suggest that there is an increased risk of RCs associated with IM ketamine in pediatric glaucoma patients undergoing EUA for IOP measurements at our institution. There is also an increased risk of RCs associated with the use of volatile anesthetics and with ASA class III/IV patients. Our study sample size is too small to make any reliable conclusions about the modifier effect of volatile agents following ketamine use (i.e., whether the use of volatile agents following ketamine additionally increased the odds of RCs). Future studies with larger sample size may be able to answer this question.

Since this is a retrospective study with a small IM ketamine sample size, it is difficult to draw any conclusions about the higher incidence of complications with IM vs IV ketamine. Based on a previous meta-analysis, we know that larger doses of ketamine are more likely to produce RCs, and this might explain our findings as the mean IM dose was higher than the corresponding IV dose of ketamine.[7] In this respect, IV ketamine has the advantage over IM ketamine in that it can be slowly titrated up to the desired anesthetic depth and thus resulting in a lower overall dose. In addition, higher doses of IM ketamine are likely to exert effects for longer periods of time, and these effects might be more likely to produce RCs when coupled with the recovery profile of superimposed volatile anesthetic agents. Finally, Melendez and Bachur[12] suggested that higher incidence of laryngospasm associated with IM ketamine may be due to inadvertent administration close to a capillary bed which results in more rapid absorption and thus a higher peak.

Our anesthetic protocol for this population has been changed to IV ketamine because of our study results. Other studies should be conducted to corroborate our findings before they can be generalized to influence the practice at other institutions.

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